

DOCKET NO.: CARP-0057**PATENT****REMARKS**

This paper is being filed following the Advisory Action dated December 2, 1999. A Notice of Appeal was filed November 29, 1999. Accordingly, it is Applicants' belief that no extension of time or accompanying fee is required. If Applicants' belief is erroneous, this serves to request the requisite extension of time and authorizes the charging of any fee to Deposit Account 23-3050.

Claims 24-31 were pending. In the Final Rejection, all pending claims were rejected. An Amendment and Request for Reconsideration ("Amendment") was filed November 3, 1999 in response to the Final Rejection. The Amendment was not entered in view of what the Examiner considered new matter in a newly submitted claim. The Advisory Action, however, indicated that the Amendment would have overcome the then outstanding rejections under 112 and for new matter of claims 24 and 28. The previous amendments to claims 24 and 28 are resubmitted herein. Their entry is earnestly requested.

New claim 49 has been added herein. New claim 49 refers to specific replacements in the heavy chain. In that regard, the Examiner is directed to Table 1 of the application as filed, specifically to the "Heavy Chain" designated as 341 b. Applicants respectfully submit that new claim 49 does not contain new matter and does not raise new 35 U.S.C. § 112, first and second paragraph issues, nor does it raise new 102/103 issues. Claim 49 is submitted herein in an abundance of caution in view of the removal of the phrase "adjacent to a CDR in the donor immunoglobulin sequence" from claims 24 and 28 as suggested by the Examiner in the Final Rejection. Claim 49 recites a specific residue that is adjacent a CDR, i.e., residue 49. If, however, Applicants' submission of claim 49 is all that stands between the application being in condition for interference, Applicants respectfully request that the Examiner so advise the undersigned at (215) 564-8352.

In view of the foregoing amendments and the arguments that follow, Applicants respectfully submit that allowable subject matter has been identified and request that the interference be declared.

The Examiner stated that the Information Disclosure Statements filed in the

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parent cases will be considered once the references are submitted. To the extent the Examiner is requiring that Applicants resubmit references already submitted, this appears to be contrary to MPEP § 609, page 600-103. Applicants are not required to resubmit references to get them considered by the Examiner.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 24-31 were again rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Applicants respectfully traverse this rejection for the reasons that follow. For the Examiner's convenience, the paragraphs are designated to correspond to the Examiner's paragraphs for the rejection remaining under this section.

a. and b. The Examiner again rejected claims 24 and 28 alleging that the specification does not provide support for the concept that only substitutions adjacent CDRs are envisaged. Claims 24 and 28 were previously amended to recite that each of the donor amino acids to be replaced is adjacent a CDR or contributes to antigen binding as determined by X-ray crystallography. During a telephone conference between the Examiner and the undersigned, the Examiner indicated that removal of the "adjacent to a CDR" language would obviate this rejection. Although Applicants disagree with the Examiner's reasoning, the claims have been amended herein to remove the recitation "adjacent to a CDR in the donor immunoglobulin sequence." As Applicants made clear in the previous response, the contribution to antigen binding need not be direct and, indeed, can be indirect, e.g., by affecting antigen binding site topology or inducing stable packing. Naturally, even for an indirect effect, the residues must be spatially near the CDR.

Applicants respectfully request that this rejection be withdrawn.

As the Examiner is aware, Applicants desire to provoke an interference between the present application and the Queen patent (U.S. Patent No. 5,585,089). Although Applicants are confident that the present claims are directed to the same invention as the

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Queen patent, new claim 49 is submitted herewith. New claim 49 recites the residues changed in example g341B disclosed in Applicants' specification as filed and, indeed, in GB8928874. Of the residues recited, all are either adjacent a CDR (49), or contribute to antigen binding as determined by X-ray crystallography (48, 71, 73, 76, 78, 88, and 91). Claim 49 is clearly allowable and clearly directed to the same invention as claim 1 of the Queen patent.

If at least one of the presented claims is not rejectable on any [] ground and is claiming the same invention as at least one claim of the patent, the examiner should proceed to initiate an interference.

MPEP 2307.02.

Applicants respectfully request that an interference between the present application and the Queen patent be declared.

Rejection Under 35 U.S.C. § 102(e)

Claims 24-31 were again rejected under 35 U.S.C. § 102(e) in view of the Queen patent. Applicants respectfully traverse this rejection. Again, the relevant inquiry as to whether the Queen patent is an appropriate reference under 102(e) is whether there is support for the claims *as allowed* in the priority applications, see MPEP 2136.03, p. 2100-85, citing *In re Wertheim*, 209 USPQ 554 (CCPA 1981), not simply whether the limitations can be found in the priority document. Regardless, Applicants maintain that the limitation "outside the Kabat and Chothia CDRs" is not found in, nor supported by, the priority documents.

This limitation requires that framework residues be changed outside both the Kabat and Chothia CDRs. This limitation is significant because the "CDRs" as defined by Kabat and Chothia differ.¹ Kabat defines CDR1 of the heavy chain as amino acids 31-35. Chothia defines the first hypervariable loop of the heavy chain as residues 26-32. As submitted in the Preliminary Amendment filed concurrently with the present application, the earliest Queen patent applications do not teach, either explicitly or implicitly, that the

¹Notably, the Chothia reference refers to loops and carefully distinguishes these loops from the Kabat CDRs.

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framework residues to be replaced by donor **must be outside both** the Kabat and Chothia CDRs. Indeed, in the specification of the Queen patent as issued, changes were made to residues inside what the Queen patent denotes as CDRH1 of Chothia, i.e., inside a Chothia CDR. Considering that the "outside the Kabat and Chothia CDRs" limitation was required for patentability, the Queen patent cannot be entitled to a priority date earlier than the filing date of the application in which this limitation was first introduced, i.e., 12/19/90.

The Examiner argued in the Final Rejection that the limitation is taught, for example, on page 9, lines 1-5 of Queen priority Application Serial No. 07/290,975 ("Queen '975") and page 13, lines 1-8 of Queen priority Application Serial No. 08/310,252 ("Queen '252"). The passages cited by the Examiner, however, do not support the Examiner's position.

The passage on page 9, lines 1-5, of Queen '975, contains a background discussion of the hypervariable regions, which it is therein stated are also called the CDRs. References by Kabat and Chothia are cited, and incorporated by reference. This is the only in passage in Queen '975 linking the Chothia reference to the term "CDRs." Other passages specifically referring to the CDRs as encompassed by the invention of Queen '975 make it clear that the CDRs are as defined by Kabat. For example, on page 10, line 2, the framework regions are defined in terms of Kabat. If the framework regions are defined in terms of Kabat, the CDRs must be as well. On page 21, the protocol for selecting which residues in the heavy chain are to be donor is set out. In lines 19-22, residues which fall in positions within a CDR "as defined by Kabat, [i.e.,] amino acids 31-35, 50-66, and 99-106" are to be donor. In lines 28-30, amino acid 30 is listed as a position **immediately adjacent to a CDR** to be changed to donor. Amino acid 30 is adjacent the heavy chain Kabat CDR, but **within** the heavy chain Chothia "CDR" as that term is used in Queen '975. The description of Figure 1 of Queen '975 indicates that it refers to the heavy chains and that the three CDRs are underlined (page 6, lines 1-6). In Figure 1, amino acids 31-35 are underlined for CDR1. Clearly, all specific references to CDRs were to Kabat CDRs only.

Further, in Figure 1, framework amino acids changed to donor are indicated by

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asterisks. Amino acids 27 and 30 are so designated. These residues are clearly within the Chothia "CDR." Neither the specification nor the claims require that more than one amino acid be changed to donor. Thus, Queen '975 teaches changing only one or two amino acids, and that both can be within the Chothia CDR. There is no support in Queen '975 for the limitation that the residues changed to donor must be outside both the Kabat and Chothia "CDRs."

Neither is there support for the limitation in Queen '252. In this instance, the passage relied upon by the Examiner for referring to Chothia is in the context of computer programs for computer models. There is no reference to CDRs. Contrastingly, the specific references to CDRs make it clear that the CDRs are as defined by Kabat. On page 8, lines 22-26, Queen '252 reports that the extents of the framework region and CDRs have been "precisely defined" by Kabat. On page 21, the protocol for selecting which residues in the heavy chain are to be donor is set out. In lines 20-22, residues which fall in positions within a CDR "as defined by Kabat, [i.e.,] amino acids 31-35, 50-66, and 99-106" are to be donor. In lines 27-29, amino acid 30 is listed as a position immediately adjacent to a CDR to be changed to donor. Amino acid 30 is adjacent the heavy chain Kabat CDR, but within the heavy chain Chothia "CDR" as that term is used in Queen '975.

Again, in Figure 1, framework amino acids changed to donor are indicated by asterisks. Amino acids 27 and 30 are so designated. These residues are clearly within the Chothia "CDR." Neither the specification nor the claims require that more than one amino acid be changed to donor. Thus, Queen '252 teaches changing only one or two amino acids to donor, and that both can be within the Chothia CDR. There is no support in Queen '252 for the limitation that the residues changed to donor must be outside both the Kabat and Chothia "CDRs."

Applicants respectfully request that this rejection be withdrawn.

The Proposed Count is the same as that submitted with the Amendment filed April 9, 1999. Applicants again identify all of the Queen parent claims 1-11 and Applicants' claims 24-31 and 49 as corresponding to the Proposed Count.

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In attached Appendix A, applicants illustrate the representative support in their present application disclosure for the limitations of their amended claim 24 and new claim 49. There is, of course, additional support in applicants' application omitted for the sake of brevity.

In attached Appendix B is a diagram of support in applicants' 1989 GB application for each limitation of applicants' amended claim 28 and new claim 49 which are also drawn to the same invention as proposed Count 1. Accordingly, applicants' effective filing date for their invention of Count 1 is 12/21/89, the filing date of their GB national application.

In view of the foregoing, Applicants respectfully submit that allowable subject matter has been identified and request that the Examiner declare an interference between the present application and the Queen patent. Specifically, the Examiner is requested to contact the undersigned at (215) 564-8352.

Respectfully submitted,



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Date: January 19, 2000

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